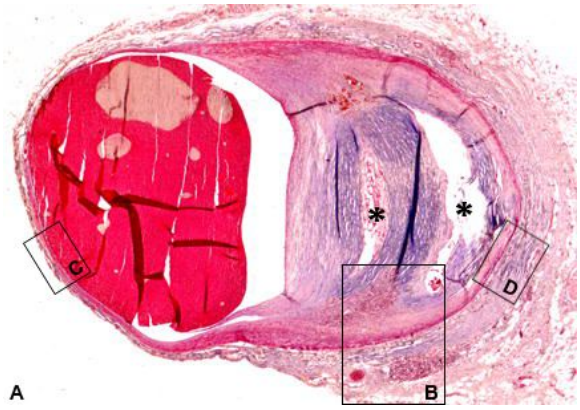
6. Adventitia – The Ultimate Defense

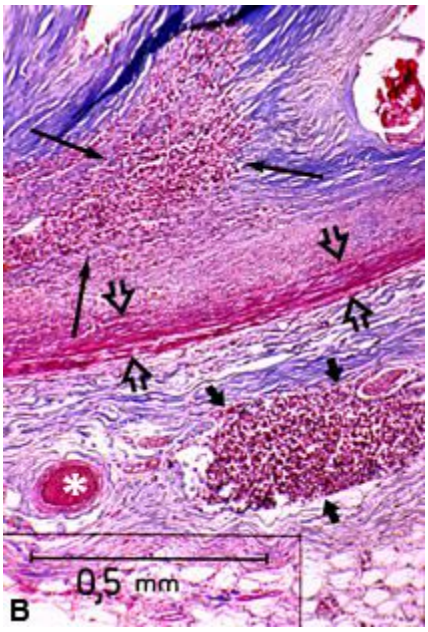
"Another feature of importance is the great tensile strength of the adventitia."
MC Winternitz, et al., [104]

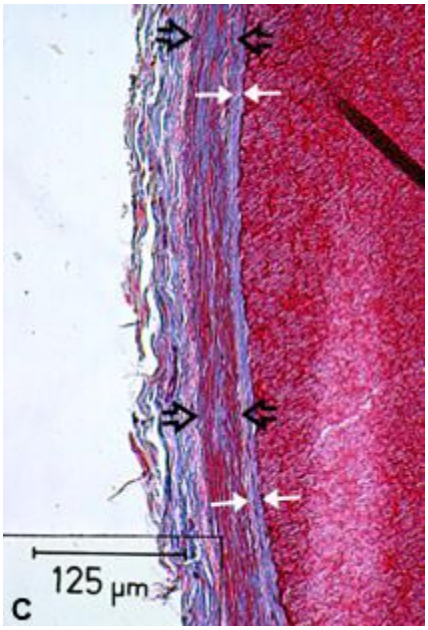
Previous chapters have shown how the IA spreads in both a longitudinal and circumferential direction within the intima. The possibility exists, judging by intimal destruction and the formation of a necrotic core, that the destructive process could also spread outward or laterally through the arterial wall, emptying plaque contents into the pericardial space. However, erosion, destruction, necrosis or perforation of the artery wall do not occur in the course of active atherosclerosis. The elastic lamina, the media, and the adventitia appear to be resistant to the effects of the IA, preventing lateral spread. Winternitz, et al. [104] showed the adventitial layer of the artery wall to be extremely strong with a very high tensile strength. It was virtually impossible, using a balloon, to rupture an artery with an intact adventitia. These same arteries were easily ruptured by removing the adventitia. The media and the elastic lamina do not compare to the adventitia in tensile strength. The adventitia may be the structure that contributes most to preventing outward growth and expansion of the IA, and may be extremely important in maintaining the integrity of the artery wall.

Adventitial Thickening over Atherosclerotic Plaques

The adventitia often thickens over atherosclerotic plaques [60], but not over unaffected artery wall, (Figures A-D). A relationship exists between the injury occurring in the intima and the resulting adventitial FP, but the precise relationship is not clear. The adventitial thickening illustrated in Figure 16 is not localized in just one area overlying the plaque, but is distributed uniformly over the entire circumference of the plaque. This diffuse thickening suggests that the IA causing intimal injury and atherosclerosis is also responsible, directly or indirectly, for producing adventitial thickening. The IA itself, or a product thereof, may diffuse or pass through to the adventitia from the plaque by direct perfusion, convection [106] or via the lymphatics, precipitating this thickening. The actual mechanism of growth may be the release of growth factors, such as Fibroblast Growth Factor, that are released by intimal macrophages and pass to the adventitia [107]. Some stimulus related to plaque formation and growth causes the adventitia to respond in a consistent, uniform, and characteristic way to the injurious process occurring in the intima.







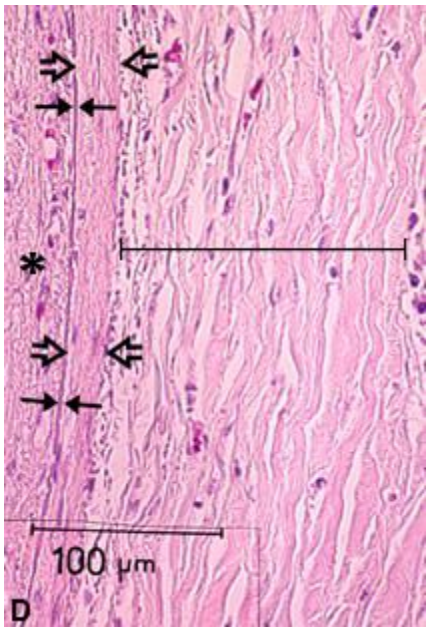


Figure 16: **A**, Proximal CIRC coronary artery from a 43-year-old white male who died in the hospital of cardiogenic shock following an AMI. The asymmetric plaque is calcified and contains two necrotic foci (asterisks), and the adventitia overlying this plaque is thickened in a rather uniform manner. The adventitia is not thickened over normal, uninvolved wall. **B**, High-power view of rectangle B in **A** showing heavy Tcell infiltrates in a thickened adventitia (short fat arrows) and associated with a similar infiltrate in the intima (long arrows). The intimal fibrous tissue adjacent to inflammatory infiltrates appears to be undergoing digestion. The media appear to be intact (open arrows). A large adventitial arteriole is close by (white asterisk). MSB stain. **C**, High-power view of rectangle C in **A**. The intima (white arrow) is of normal thickness and is not involved with atherosclerosis. The media (open arrow) and the adventitia appear normal without injury, thickening, inflammation, or increased vascularity. MSB stain. **D**, High-power view of rectangle D in **A**, containing a small portion of the intima (asterisk), the internal elastic lamina (solid arrows), the media (open arrows), and the adventitia (bracket). The adventitia is composed of layers of thick collagen fibers, often wavy in appearance and oriented in a circumferential direction. Relatively few cells are present and typical intimal SMCs cannot be identified in the adventitia. H & E stain.

Evolutionary Purpose of Adventitial Thickening

Why should the adventitia thicken when the primary injury involves the intima? Shi, et al. [108] demonstrated adventitial thickening following balloon injury

to the coronary arteries in pigs. They noted striking similarities between ordinary wound healing and the adventitial response to injury. In circumstances of traumatic injury, clearly the adventitia plays a key role in resolution and repair, with fibromyoblasts migrating to the intima [108]. Perhaps the adventitial thickening associated with active atherosclerosis is produced in response to intimal injury, particularly to progressive and expanding injury by the IA.

What role or what evolutionary purpose does adventitial thickening play in atherosclerosis? Is adventitial thickening a pathologic response that should be prevented, or is it a physiologic response to injury? The most logical explanation is that the thickening is a physiologic, defensive response to outward spread and expansion of the IA, similar to the FP response observed in many chronic inflammatory conditions [109].

Adventitial Resistence to the IA

Fibroblasts, not SMC, are the predominant cells of the adventitia. They do not succumb to the IA, do not transform into macrophages, and do not produce an abnormal form of extracellular matrix that reacts with and retains lipid. Lipid-laden macrophages, foam cells, or excessive amounts of extracellular lipid are not a prominent feature of the adventitial thickening over plaques, and lipid-laden SMC are not present in these areas (Figure 16D). Adventitial cells and tissue do not contribute to the destructive process and do not undergo degeneration or necrosis as the disease advances. Therefore, unlike monocyte macrophages and intimal SMC, the adventitial fibroblast does not become a component of active atherosclerotic disease. The failure of atheromas to erode through the adventitia and ulcerate into the pericardial space, and the failure of a necrotic core to form in the adventitia indicate an inherent resistance of the adventi tia to the aggressive, destructive effects of the IA. The adventitia is an extremely strong barrier that, in essence, serves to restrict the IA to the intima, where the only outlet for the expanding necrotic core is into the arterial lumen.

Histologic Features of Adventitial Thickening

What characteristics of the adventitia combine to make it resistant to atherosclerotic injury? Typical features of adventitial thickening, shown in Figures 16A and 16D, are tight, thick layers of sparsely cellular collagen, wavy in appearance and oriented, band-like fashion, circumferentially around the artery. These histologic features are markedly different from the intimal FP response shown in Figures 3A and 3B. There are significant structural differences between the fibrous tissues of the intima and the adventitia to support the observed differences in their physiologic responses.

Adventitial fibrous tissue has been termed “fibrillar collagen” [10] because of its thick fibers, and because it has been shown to be relatively stiff, hard, and rigid compared with the fibrous tissue of the intima, producing a stiff collar around the artery [10,108). Some of this stiffness may be related to differences in the amount and composition of the ECM. Intimal fibrous tissue has a higher content of PGs and is more visco-elastic and compressible than the adventitia where the PG content is quite low [43]. These different physical characteristics of tissue may impart tensile strength to the adventitia and may also contribute to its inherent resistance to the IA.

Significance

The adventitial FP response and inherent resistance to the IA may have teleological significance because preservation of arterial wall integrity is more important to the organism than preserving the

luminal diameter of the artery. In other words, loss of arterial wall integrity by the IA's eroding through to the pericardial space means certain death, but loss of luminal diameter due to the activity of the IA that is confined to the intima may be tolerated and be compatible with life. Adventitial thickening, the infiltration of T lymphs into the adventitia, and the marked increase in vascularity due to the profuse development of the vasa vasorum may be physiologic responses that limit the growth and expansion of the IA.

In Review

The adventitia is resistant to the IA causing atherosclerosis, and it prevents the destructive process from eroding outward through the arterial wall into the pericardial space. The adventitia thickens and acts to maintain wall integrity as well as to confine the IA to the intima, where the only outlet for the necrotic core is into the artery lumen. Adventitial fibroblasts and adventitial collagen are not affected or subverted by the IA and they do not contribute to the growth and expansion of the disease process.